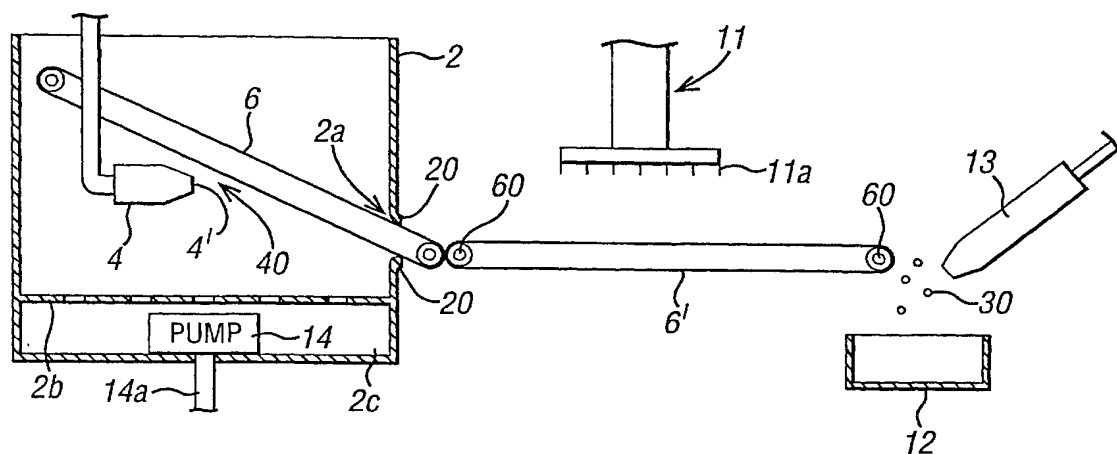




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61J 3/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/67694</b> <b>(43) International Publication Date:</b> 16 November 2000 (16.11.00)
<b>(21) International Application Number:</b> PCT/GB00/01728 <b>(22) International Filing Date:</b> 5 May 2000 (05.05.00)  <b>(30) Priority Data:</b> 9910505.8      6 May 1999 (06.05.99)      GB  <b>(71) Applicant (for all designated States except US):</b> ELEC-TROSOLS LTD. [GB/GB]; Thursley Copse, Farnham Lane, Haslemere, Surrey GU27 1HA (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> COFFEE, Ronald, Alan [GB/GB]; Longdene House, Haslemere, Surrey GU27 2PH (GB). PIRRIE, Alastair, Bruce [GB/GB]; 91 Plantation Road, Oxford OX2 6JE (GB).  <b>(74) Agents:</b> BERESFORD, Keith, Denis, Lewis et al.; Beresford & Co., 2-5 Warwick Court, High Holborn, London WC1R 5DJ (GB).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** A METHOD AND APPARATUS FOR MANUFACTURING DISSOLVABLE TABLETS



**(57) Abstract**

Consumable or dissolvable tablets are manufactured by: supplying a liquid containing a biodissolvable carrier to an outlet (41); establishing an electric field between the outlet (41) and a support surface (6) to cause liquid issuing from the outlet to form at least one fibre or fibrils of the biodissolvable carrier which fibre or fibrils deposit(s) onto the surface to form a fibre web or mat; separating the web or mat into a plurality of individual tablets; and incorporating at least one active ingredient on or in the tablets.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

A METHOD AND APPARATUS FOR MANUFACTURING  
DISSOLVABLE TABLETS

5       This invention relates to a method and apparatus for manufacturing dissolvable tablets especially, but not exclusively, dissolvable tablets carrying at least one pharmacologically or biologically active ingredient for therapeutic or prophylactic treatment of an animal such as a human being.

10       Conventional medicines to be ingested in a solid form are manufactured as a compressed solid tablet or a capsule containing granules which when swallowed enter into the blood stream via the gastro-intestinal tract. Some patients have, however, difficulty in swallowing  
15       tablets or capsules. To address this problem and/or to cause the active ingredient to dissolve at the oral mucosa so that it enters the blood stream without entering the gastro intestinal tract, tablets or pills that dissolve on the tongue or in the mouth have been  
20       manufactured. This enables buccal delivery of drugs which is especially advantageous where the drug is intended to be delivered to the central nervous system because it enables rapid delivery of the drug to the brain and avoids or at least inhibits delivery of the drug to the  
25       non-targetted areas such as the gastro-intestinal tract where the presence of the drug may have disadvantageous side effects. Also, drug absorption through the blood-rich epithelium in the mouth, rather than the chemically

hostile environment of the stomach and the intestine may generally be advantageous.

Such quick dissolving tablets are conventionally formed by dissolving food or pharmacological grade gelatin to form a gelatin solution. The gelatin solution is then frozen solid converting the water content into ice. The unbound ice is then removed under conditions of low pressure which cause the ice crystals to sublime, turning them directly into water vapour which is collected by a water vapour condenser. The vacuum encourages the orderly migration of water vapour to the condenser and so as to assure that the pressure of the water vapour remains below its triple point as is required for sublimation to occur. Secondary drying is then required to remove the tightly bound (sorbed) water that is strongly attached to the protein molecules. This tightly bound water is difficult to remove because it has a lower vapour pressure than free liquid at the same temperature. Accordingly this secondary drying is a slow process.

The initial rigid ice matrix of the frozen sample and the exceptionally gentle drying ensure that the dried resulting product maintains its structural integrity.

The above described process results in tablets or pills that regularly dissolve or disintegrate in the mouth or on the tongue. However, the process described above is a relatively complex process and generally has to be carried out as a batch-by-batch process.

It is the aim of the present invention to provide apparatus for and a method of manufacturing dissolvable tablets that may dissolve or disintegrate rapidly in the mouth, on the tongue or on any wet surface or in a wet environment, suitable for continuous mass production.

In one aspect, the present invention provides a method of manufacturing dissolvable tablets which comprises using electrohydrodynamic comminution to form a plurality of individual tablets or pills, with each tablet consisting of a fibre web or mat which will dissolve or disintegrate on the tongue or in the mouth of a consumer such as a patient.

The tablets or pills may carry an active ingredient which may be, for example, a drug or other therapeutic agent. The active ingredient may be: carried by (for example in solution with) the liquid or molten material used to form the fibres; provided by electrostatically coating the mat or individual tablets or pills with charged particles; provided by providing the fibres as cored fibres with the core containing the active ingredient; or provided by spraying the fibres after or during deposition with oppositely charged particles of the active ingredient so as to form alternate layers of fibres and the active ingredient. One or more of these techniques may be used to form a particular tablet and different active ingredients may be incorporated into the same tablet. For example, where the tablets are formed by a sandwich of alternate layers of fibres and the active ingredient, the composition of the different layers of

active ingredients may be different. In addition, the composition of the fibres forming each of the layers of fibres may be different. This would allow, for example, controlled release of different active ingredients enabling, for example, buccal delivery of a first active ingredient and then later delivery in the gastro-intestinal tract of the same or a different active ingredient, so enabling, for example, sustained or controlled delivery of a drug or other active ingredient or controlled multiple drug therapy.

A method embodying the invention should enable accurate doses of an active ingredient such as a drug to be delivered to any wet surface in a form which is easy and convenient to handle, for example: the application of a growth factor or other compound to an open wound where a pad or tablet would quickly dissolve and release an even distribution of an active ingredient to the surface of the wound; or the delivery of a local anaesthetic to an eye ball after surgery; or delivery of drugs to any animal; or even reconstitution of a dried drug for dissolution in water such as for injection, drinking or eating with food.

The fibres may be formed using any suitable biologically acceptable or compatible polymer that is hydrophilic so that, on contact with a wet surface, it effectively deliquesces becoming liquid by absorbing the water, thereby dissolving. Suitable such polymers include food grade gelatins, polyvinyl pyridine, polyvinyl alcohol, polysucrose, other polysaccharides such as

starch and cellulose and its derivatives, sugars and confectionary mixtures such as toffee and caramel and any other biologically compatible products that can be formulated into a liquid solution suitable for use in the electrohydrodynamic comminution process or can be made liquid by the application of heat.

Embodiments of the present invention will now be described, by way of example, with reference to the accompanying drawings in which:

Figure 1 shows a part sectional very schematic side view of apparatus embodying the invention;

Figure 2 shows a part sectional view taken along the line II-II in Figure 1;

Figure 3 shows a very schematic part sectional view of a modified form of the apparatus shown in Figure 1;

Figure 4 shows very schematically a further modification of the apparatus shown in Figure 1;

Figure 5 shows a part sectional very diagrammatic view of a further modification of the apparatus;

Figure 6 shows diagrammatically a modified form of comminution arrangement for use in the apparatus shown in any of Figures 1 to 5;

Figures 7 to 9 show electronmicrographs with Figures 7 and 8 illustrating the structure of a tablet produced by the conventional freeze gelling technique and Figure 9 illustrating the structure of a tablet produced using a method embodying the present invention.

Referring now to the drawings, the apparatus 1 shown in Figure 1 consists of a container 2 made of thermally insulative material such as a glass, or a plastics material such as Perspex (trade mark).

5        A comminution arrangement 3 is mounted within the chamber 2. The comminution arrangement 3 comprises a hollow tube 4 having an outlet nozzle 4'. The tube 4 is electrically conductive at least adjacent its nozzle 4'. The electrically conductive nozzle 4' is coupled to the  
10        earth terminal E of a high voltage source or supply 5 mounted outside the chamber 2. The high voltage terminal 5a of the high voltage supply 5 is coupled to a corona discharge electrode 50 for charging a support surface 6 disposed opposite the outlet nozzle 4a so as to enable an  
15        electric field to be established between the nozzle 4a and the support surface 6. Other ways of charging the support surface 6 such as a brush contact may be used, but the use of a corona discharge electrode 50 has the advantage of avoiding arcing and subsequent erosion.

20        The support surface 6 is in the form of a conveyor belt supported along its length (see Figure 2) by rollers 60 rotably mounted to supports (not shown) such that, as shown most clearly by Figure 2, the conveyor belt 6 extends at an angle to the horizontal. One of the  
25        rollers 60 is fixedly mounted to the spindle 7a of a drive motor 7 mounted outside the chamber 2.

As shown in Figure 2, the conveyor belt extends through an aperture 2a provided in the chamber 2. To maintain the environment within the chamber 2a and to



assist in formation of the tablets as will be described below, the aperture 2a has flexible lips 20 formed of a rubber or plastics material which press onto the surface of the conveyor belt 6. An environmental control unit 8  
5 may be mounted within the chamber so as to direct enable control of the temperature of the air in the region 40 where liquid issuing from the nozzle 4a is subject to the electric field established between the nozzle 4a and the support surface 6.

10 A perforate wall 2b of the chamber 2 separates the main chamber from a subsidiary chamber 2c which houses an exhaust pump 14. The exhaust pump 14 has an outlet 14a for exhausting air to the outside of the chamber 2.

A biologically acceptable carrier liquid is supplied  
15 to the tube 4 from a liquid supply reservoir 9 mounted outside the chamber 2 by means of a pump 10. The temperature of the reservoir 9 may be controlled so that its contents are thermally adjusted to produce fibres when sprayed. For example a solid may be heated to a  
20 liquid state ("melt") to be sprayed, or an inviscid liquid may be cooled to make it more viscous. In this way the range of products and formulations that can be sprayed may be extended beyond liquids that are sprayable at room temperature and may avoid the need for solvents.

25 As shown in Figure 2 a horizontal further conveyor belt 6' is supported on rollers 60 adjacent the conveyor belt 6 so that in known manner material can pass directly from the conveyor belt 6 to the conveyor belt 6'. A cutting device 11 is mounted above the further conveyor

belt 6' outside of the chamber 2 so that a matrix of cutting blades 11a of the cutting device are moveable towards and away from the conveyor belt. A hopper 12 is mounted beneath the end of the conveyor belt to receive the resulting tablets or pills.

As shown in Figure 2, a spraying device 13 may be provided at the end of the further conveyor belt to spray the resulting tablets with a final coating as will be explained below.

In use of the apparatus shown in Figure 1, the high voltage 5 is first switched on to establish an electric field between the nozzle 4' and the support surface 6. Typically, the high voltage applied to the support surface or spindle 6 will be approximately 20 kilovolts. Applying the high voltage to the support surface 6 and earthing the nozzle 4' acts to focus the electric field and produce less erratic spraying than would sometimes be produced if the high voltage was applied to the nozzle 4' and the surface 6 was earthed. The drive motor 7 and pump 14 are then activated so as to rotate or drive the conveyor belt 6'. If required, as environmental control unit 8 may be used to adjust the ambient temperature so that either warm or cold air, dried or humidified flows through the chamber 2. The temperature of the air within the chamber 2 will be controlled to be appropriate for the formulation being sprayed. For example, the temperature may be controlled to have a value between 0°C and 200°C, depending on the formulation being sprayed. The temperature may, depending upon the formulation being

sprayed, be in the range of 30°C to 200°C or 50°C to 100°C.

The liquid pump 10 is then activated to pump liquid to the tube at a rate of between 1 and 20ml, for example  
5 about 4ml (millilitres), per hour.

Liquid issuing from the output nozzle 4' forms, under the influence of the applied electric field, a Taylor cone and jet which solidifies to form a fibre which is attracted to and deposits on the support surface  
10 6 as a fibrous web or mat. The speed of movement of the conveyor belt 6 is typically less than 1 metre/second ( $\text{ms}^{-1}$ ). A conveyor belt 1 metre wide moving at 5mm/s or 0.005 m/s should enable 100,000 tablets with a surface area of  $2\text{cm}^2$  to be produced per hour.

15 The mat or web is moved away from the area of the high electric field by the conveyor belt, is squeezed slightly against the conveyor belt 6 by the resilient lips 20 which act to compress the fibre mat or web slightly and then transferred to the further conveyor  
20 belt 6'.

The cutting device 11 is reciprocated towards and away from the further conveyor belt 6' by conventional reciprocating means (not shown) in synchronism with the movement of the belt so that the cutting blades 11a of  
25 the cutting device cut the compressed mat or web into tablets or pills 30. Although not shown, a printing stage may be provided for printing information such as a logo or dosage amount on the tablets. The tablets or pills 30

then drop off the end of the further conveyor belt 6' and are collected in the hopper 12.

As noted above, a spraying device 13 may be provided to coat the individual tablets or pills 30 with, for example, a sugar coating. The spraying device 13 may be a conventional spraying device or may be an electrohydrodynamic spraying device of the same type as the comminution arrangement 3.

Typically the gap between the outlet nozzle 4 and the support surface 6 is about 1 to 20 cm.

The use of the conveyor belt arrangement enables a continuous process and also allows the highly charged fibre web or mat to be moved away from the area of the electric field leaving a more appealing lower charged surface behind to facilitate the deposition of further material. In the arrangement described above, the nozzle 4' is arranged to spray horizontally onto the conveyor belt 6 which is arranged at an angle to the horizontal. This has the advantage that any undesired large or satellite droplets issuing from the nozzle 4' will, due to the influence of gravity, fall away from both the nozzle 4' and the conveyor belt 6. Where the possibility of satellite droplets is small and does not present a problem then the conveyor belt 6 may extend horizontally and the nozzle 4' may be arranged above or below the conveyor belt 6 so as to spray directly downwardly or upwardly, respectively, onto the conveyor belt 6.

The liquid supplied to the tube 4 may contain a pharmacologically or biologically active ingredient such

as a drug or medicament to be imbibed by the patient, especially drugs acting upon the central nervous system where buccal delivery via the mouth mucosa will have specific benefits and/or where entry into the body via the gastro-intestinal tract is to be minimised for physiological reasons, for example to inhibit adverse side effects. Examples of such drugs are eletriptan and sildenafil.

As an example, the biologically acceptable carrier may be gelatin. Experiments to determine the optimum gelatin-based formulation for achieving a tablet which will maintain its shape but will dissolve or disintegrate readily on the tongue were carried out. These experiments were carried out using an annular nozzle which, for convenience, was arranged to spray onto a slowly rotating (for example 1 revolution/hour) 350 mm diameter metal plate rather than onto the conveyor belt. The nozzle 4' was separated from the plate by a distance which was varied between 60 and 200 mm and a voltage of between 25 and 30 kV was applied to the plate. Generally 30 kV was applied to the plate. The liquid to be sprayed to produce the desired tablets was supplied to the nozzle 4' with a flow rate between 10 and 20 ml per hour.

In this case, the liquid to be sprayed consisted of CRODA spray dried fish gelatin with the solvent being a water-ethanol mix. In the experiments, formulations were investigated in which 5g of the fish gelatin was

dissolved in between 17 and 30 ml of the water-ethanol solvent.

It was found that the spray performance of the formulation was affected by the overall ratio of water to ethanol content and also by the overall viscosity of the solution. The ratio of water to ethanol was varied between 2:1 and 1:2. It was found that a higher ethanol content produces a more sprayable solution but that an excess of ethanol causes the gelatin to precipitate out of solution with it being impossible to properly dissolve the 5g of gelatin in an 8 ml water : 12 ml ethanol (2:3) solvent mix. It was also found that a high proportion of water provides a more stable solution that is more difficult to spray and also produces a slightly wetter product that is more likely to contain droplets in addition to the desired fibre. The best formulations were found to have a solvent consisting of 7 to 9 ml of water and 10 to 11 ml of ethanol. The current preferred formulation is 8 ml of water, 10 ml of ethanol, 1 ml of peppermint flavouring (which is a mixture of water and isopropanol plus the flavouring) and 5g of the spray dried fish gelatin.

The less viscous solutions (that is where there was 22 to 30 ml of solvent per 5g of fish gelatin) sprayed in a more stable fashion but tended to produce droplets and some beaded fibres. In contrast, more viscous solutions having 17 to 21 ml of the solvent produced the desired distinct fibres and resulted in tablets having only a little friability.

Increasing the distance between the nozzle 4' and the support surface onto which spraying was being effected increased the likelihood of fibre formation (because it allowed further time for evaporation of the solvent) and made the resultant tablet more fibrous and friable. In contrast, placing the nozzle 4' very close (60 to 70 mm) to the support surface had the opposite effect with the solvent having less chance to evaporate and thus encouraging a less friable but more dense product. As a result of these experiments, it was found that the optimum distance for spraying the current preferred formulation to achieve the desired low density low friability tablets was a separation of between 100 and 200 mm between the nozzle 4' and the plate with the actual distance within this range being fairly flexible.

The addition of sweeteners to increase the palatability of the tablet was investigated. It was found that the addition of a little (50 mg or so) of saccharine to the liquid resulted in no noticeable effect on the end tablet apart from the desired sweetness. Surprisingly, however, when a similar quantity of d-sorbitol (mannitol) was added, it was found that the tablets shrank catastrophically over a day or, so resulting in a high density rubber-like structure which would not dissolve readily in the mouth or on the tongue.

Other grades of gelatin may be used to adjust the physical properties of the product. For instance, a product made purely from fish gelatin dissolves extremely quickly in water but can also be dissolved by sweat on

the fingers. Although this problem can be countered by a thin coating applied to the finished pill or tablets, other less soluble gelatine grades may be used instead of, or as well, as the fish gelatin to make it more robust and less fryable. Also the degree of spray drying of the gelatin may affect the characteristics of the end product.

Further experiments have shown that many other formulations may be used which do not contain animal products and are therefor suitable for vegetarians. These will include alternative solutes such as polyvinyl pyridine, polyvinyl alcohol, poly-sucrose, other polysaccharides, such as starch and cellulose and its derivatives, sugars and confectionery mixtures, such as toffee and caramel, and other biologically compatible products that can be formulated into a liquid solution or made liquid through the application of heat and which will dissolve or melt on contact with wet surfaces as required. Mixtures of different polymers may also be used, for example a small quantity of another biologically acceptable polymer may be added to a gelatin formulation to improve its performance.

The following table gives specific examples of polymer formulations that may be used as the biologically acceptable carrier. In this table the flow rate column indicates the flow rate from the outlet of the supply tube, the voltage indicates the voltage difference between the outlet tube and the conveyor belt used to cause electrohydrodynamic spraying and the comments



column indicates the spray properties and characteristics of the resulting web or mat product. The separation is the distance of the supply tube outlet from the conveyor belt and "Mw" is the molecular weight.

5

10

15

Polymer	Formulation	Flow Rate	Voltage (kV)	Separation (at room temperature)	Comments
"Luviskol" a vinylpyrrolidone/vinylacetate copolymer  Manufactured by BASF, 67056 Ludwigshafen Germany	Luviskol is provided as a 50% solid in ethanol solution. This in turn is diluted with extra ethanol in a ratio of two parts of Luviskol to one part of ethanol	upto 30 ml/hr	15 kV	Wide range from 5cm to 15 cm	Very stable spray. Build up fairly rapid. Product very soluble. Large fibres.
Polyvinylpyrrolidone	Mw 360,000: 0.5g in 10ml ethanol	upto 20 ml/hr	15 - 20kV	Wide range from 5cm to 15cm	Very stable. Not a very rapid build up of product
Gelatin	5g in: 8ml water, 12ml ethanol	upto 30 ml/hr	20-30kV	Wide range from 5cm to 15cm	Not very stable. However rapid build up of web. Product is very soluble in water

Polymer	Formulation	Flow Rate	Voltage (kV)	Separation (at room temperature)	Comments
Polyvinyl-alcohol	Mw 100,000 and 130,000. Concentration of 0.1g/ml in 1:1 water and ethanol	10ml/hr	14 - 20kV	6 to 10cm	Very stable, very soluble in water. Lower molecular weights produce denser product, which is less soluble, and higher molecular weights are too viscous.
5 "Luvitec VPI 55" vinylpyrrolidone/ vinylimidazole copolymer 10 Manufactured by BASF	~4g in 10ml ethanol	5ml/hr	12kV	9cm	Multi-jets, very soluble loosely packed mat. Very tacky. Stable. Possible to make more concentrated.

Figure 3 is a view similar to Figure 2 showing a modification of the arrangement shown in Figure 2. As can be seen from Figure 3, the apparatus 1a shown in Figure 3 differs from that shown in Figures 1 and 2 in that the sprayer 13 is provided within the chamber 2 and is arranged so as to direct a spray at liquid issuing from the nozzle 4a so that the fibre is coated as it is formed. Figure 3 also shows a spraying liquid reservoir 13a and pump 13b.

In the embodiments described above, the tablets or pills are formed using the cutting device 11. Different forms of cutting devices may, of course, be used. For

example, a pair of reciprocating knives may be provided one on either side of the conveyor belt each arranged to cut at an angle to the length of the conveyor belt so as to produce lozenge shaped tablets or a rolling blade may be used. As another, possibility, a cutter defining a plurality of tablet or pill shapes may be used which is lowered onto the fibrous mat to cut an area of the fibrous mat into an array of pill or tablet shapes. By applying suction to the cutting device, the cut shapes may then be lifted from the fibrous mat by the cutting device and transferred to and aligned with a blister pack base. Once the cutting device has been correctly positioned over the blister pack base, then the suction pressure may be reversed so as to blow the tablets gently into respective receptacles in the blister pack base. This cutting device may be arranged to cut out the pills or tablets so that they have a circular or oval shape. To minimise wastage, the cutting device may, alternatively, be arranged to cut out the tablets so that they have a rectangular or hexagonal shape with the corners of the rectangles or hexagons being rounded.

In the apparatus described above, the fibres are formed using a single cylindrical liquid supply tube 4 having an annular outlet nozzle 4'. However, the apparatus may be provided with an array of such liquid supply tubes extending transversely of the direction of movement of the conveyor belt 6 or even with a matrix of such liquid supply tubes. Where such an array is used, then the separate liquid supply tubes each provide a

comminution site. In order to avoid interference effects between the separate comminution sites, the spray heads should be separated by a distance of at least 10 to 20 cm, or provided with electrostatic screening electrodes. Alternatively or additionally, a slot-like nozzle may be used.

In addition, or as an alternative, a number of liquid supply tubes may be arranged along the length of the conveyor belt. Typically, the spacing between liquid supply tubes in this longitudinal direction should be 20 to 40 cm, for example 30 cm, although they may be placed closer together if the individual liquid supply tubes are electrostatically screened. Figure 4 illustrates very diagrammatically a modification of the apparatus shown in Figures 1 and 2 wherein nine liquid supply tubes 4a to 4i are arranged so as to extend along the length of the conveyor belt 6. As shown in Figure 4, each liquid supply tube is connected to a respective liquid supply pipe 10a to 10i to which liquid is pumped via a corresponding pump (not shown) from a corresponding reservoir (not shown). Thus, each of the liquid supply tubes 4a to 4i will be coupled via a liquid supply pipe and pump to a reservoir in the manner similar to that shown in Figure 1 for the liquid supply tube 4.

Providing a plurality of liquid supply tubes along the length of the conveyer belt has a number of advantages. In particular, it enables different liquids to be supplied via the different liquid supply tubes 4a to 4i. As one example, alternate liquid supply tubes 4a,

4c, 4e and 4g may supply the polymer liquid formulation discussed above while the intervening liquid supply tubes 4b, 4d, 4f and 4h may supply a tacky ingredient such as gum arabic or gum tragacanth to facilitate adhesion of the fibres to one another and the final liquid supply tube 4i may supply a flavouring or sugar coating. Also, the use of a plurality of nozzles supplying different liquids enables, for example, active ingredients which are lypophilic as opposed to hydrophilic to be incorporated into the tablets.

To further facilitate adhesion of the fibres to one another and to make the resulting product less fluffy, if required, the nozzles of alternate liquid supply tubes may be charged to opposite polarities. In addition, one or more of the liquid supply tubes 4a to 4i may be replaced by a spraying device which sprays charged dry powder of the opposite polarity to the fibres so that the dry powder is attracted to and sticks to the fibre. Such a dry powder may contain an active ingredient or ingredients for the tablet and/or flavourings or colorings. One advantageous way of producing such electrically charged dry powder would be to use the triboelectric charging process. Another way would be to use ionic bombardment. Both these techniques are well known. The ionic bombardment process provides a copious supply of ions which are attracted directly to the fibres and may be desirable in order to reduce the charge on the sprayed mat.

Typically, it is possible to achieve charge of the order of 1 coulomb per kilogram when producing the fibres from liquid but charge of only the order of  $10^{-3}$  coulombs per kilogram for dry powder. Thus, if the dry powder is produced to be of the opposite polarity from the fibres, then the overall mat before separation into the tablets will still be charged to the polarity of the fibres but will have an overall reduced charge. This enables a large amount of oppositely charged particles to be applied to the spray mat.

In an embodiment, the liquid supply tubes arranged along the length of the conveyor belt may be arranged so as to provide, alternately, a supply of fibres and a supply of an active ingredient with opposite plurality voltages being applied to longitudinally adjacent liquid supply tubes so that a layer of fibres of one polarity is deposited followed by a layer of active ingredient of the opposite polarity followed by a layer of fibres of the one polarity followed by a layer of active ingredient of the other polarity and so on to the desired thickness. Different active ingredients may be provided in the different active ingredient layers and different fibres or fibre thicknesses may be provided in the different fibre layers. This may allow, for example, a multiple therapy tablet to be produced which enables, for example, rapid buccal delivery of one active ingredient and slower delivery via the gastro intestinal tract of the same or a different active ingredient.

As described above, an environmental control unit may be provided to control temperature and/or humidity. Where a plurality of liquid supply tubes spaced apart along the length of the conveyor belt are provided then  
5 each liquid supply tube may be provided with its own local environmental control unit which may be provided, for example, immediately downstream of the liquid supply tube to allow, for example, for drying of the just-formed layer prior to deposition of further material on that  
10 layer.

Another way of electrically compacting the product is to apply alternating polarities to the spray nozzles over time. The frequency would typically be quite low so the electrohydrodynamic process has time to adjust.  
15 Frequencies below 10Hz are preferable.

Figure 5 illustrates very diagrammatically a further modification of the apparatus described above. In this example, the conveyor belt 6 is horizontally arranged, but the further conveyor belt 6' and the cutting device  
20 11 are omitted and a field controlling arrangement is provided so as to direct the fibres only towards certain areas of the surface 6. As shown, this is achieved by provided on the surface of the conveyor belt 6 a tray-like arrangement 16 having a regular array of tablet or  
25 pill sized and shaped recesses 16. The tray-like arrangement is designed so that the interior surface of each recess 16b is positively charged while the islands 16a between the recesses are negatively charged.

In this arrangement, the nozzle 4' is arranged to be negatively charged and the belt earthed by the high voltage source 5 so that the material issuing from the nozzle is negatively charged and thus will be attracted into the recesses 16b but repelled from the islands 16a so that a series of individual tablet sized mats or webs of fibres are produced. Where non-gelatinous products are used the spray distance can be much reduced to around 1 to 2cm, and in such cases the nozzle can be placed just above, making it easier to direct the spray into the well.

Figure 6 illustrates that schematically a further modification which may be made to the comminution arrangement 3. The arrangement 3a shown in Figure 6 has two reservoirs 9a and 9b containing different liquids each coupled by a respective valve V1 and V3, a respective pump 10a and 10b and a further valve DV and V4 to a respective outlet nozzle 4'1 and 4'2. This arrangement enables a first liquid to be provided within a curtain of the second liquid enabling a cord or coated fibre to be produced. It would be appreciated that Figure 6 is only very schematic. Further details of an arrangement for enabling a first liquid to be supplied within a second liquid are described in WO 98/03267 (see especially Figures 11 and 14) the whole contents of which are hereby incorporated by reference.

Figures 7 to 9 are electronmicrographs showing in Figures 7 and 8 the structure of a conventional freeze dried tablet and in Figure 9 the mat or web like fibre



structure of a tablet produced using the apparatus shown in Figures 1 and 2 and the gelatin solution mentioned above. As can be seen, the resulting fibre consists of a fine mat or web of strains or fibres which appear to be simply individual strands of rapidly dried polypeptide chains that have become entangled to form strands or fibrils. These in turn would appear to have become entangled with one another forming strings which themselves become intertwined to form rope like structures which overlay one another to form a fibrous cotton wool like material. This very open fibre structure can be fully hydrolysed in the mouth with full breakdown of the secondary structure so that the fibres become disentangled but will not form junctions zones which would result in gelling of the product which would be undesirable.

The active ingredient or ingredients to be supplied by consumption of a tablet or pill produced using the apparatus described above may be any agent or substance which provides a desired effect in the consumer. For example, the active ingredient may be a medicament for use in the treatment by way of therapy, surgery or diagnosis or otherwise to improve quality of life of a human being or other animals. For example, the active ingredient may be nicotine, morphine, a vitamin, an antiseptic, an anti-inflammatory, an antibiotic, an anti-cancer agent or other pharmaceutical product, a vaccine, a protein, or an enzyme.

The present invention also has applications outside the medical field. Thus, the apparatus described above may be used to produce confectionary products which melt in the mouth. In such cases, the active ingredients may  
5 comprise at least one or more of the following: a flavouring; chocolate; a colorant; and a sweetener.

The fibres may be formed using any suitable biologically acceptable or compatible polymer that is hydrophilic so that, on contact with a wet surface, it  
10 effectively deliquesces becoming liquid by absorbing the water, thereby dissolving. Suitable such polymers include food grade gelatins, polyvinyl pyridine, polyvinyl alcohol, polysucrose, other polysaccharides such as starch and cellulose and its derivatives, sugars and  
15 confectionary mixtures such as toffee and caramel and any other biologically compatible products that can be formulated into a liquid solution suitable for use in the electrohydrodynamic comminution process or can be made liquid to the application of heat.

20 As used herein the term "biodissolvable" means capable of being dissolved or disintegrated in the mouth or on the tongue of a human being or other animal and on another wet surface such as an open wound where the pad or tablet would dissolve quickly to release a drug or  
25 other product onto the surface of the wound or an eye ball surface to deliver for example, a local anaesthetic to the eye ball after surgery. Tablets manufactured by a method in accordance with the invention may also be

provided so as to be reconstituted in water for injection or drinking or eating with food for example.

Other modifications will be apparent to the skilled person in the art.

**CLAIMS:**

1. A method of manufacturing consumable or dissolvable tablets, comprising:

5 supplying a liquid containing a biodissolvable carrier to an outlet;

establishing an electric field between the outlet and a support surface to cause liquid issuing from the outlet to form at least one fibre or fibrils of the  
10 biodissolvable carrier which fibre or fibrils deposit(s) onto the surface to form a fibre web or mat;

separating the web or mat into a plurality of individual tablets; and

incorporating at least one active ingredient in  
15 and/or the tablets.

2. A method according to claim 1, which comprising:

separating the web or mat into a plurality of individual tablets by cutting the web or mat.

20

3. A method of manufacturing tablets, comprising:

supplying to an outlet a liquid containing a hydrophilic biologically compatible carrier which melts or liquifies on contact with a wet surface;

25 establishing an electric field between the outlet and a support surface to cause liquid issuing from the outlet to form at least one fibre or fibrils of the carrier;

causing the at least one fibre or fibrils to deposit onto the surface to form a plurality of individual tablets each comprising a fibre web or mat; and

providing the tablets with at least one active  
5 ingredient.

4. A method according to any one of the proceeding claims, which comprises supplying to provide the liquid a composition comprising at least one of a gelatin,  
10 polyvinyl pyridine, polyvinyl alcohol, poly-sucrose, starch, cellulose, a cellulose derivative, a sugar, a confectionary product such as toffee or caramel.

5. A method according to any one of claims 1 to 3,  
15 which comprises supplying as the liquid a solution consisting essentially of 5 grams of fish gelatin in a solvent consisting of from 7 to 9 millilitres of water and 10 to 11 millilitres of ethanol.

20 6. A method according to any one of claims 1 to 3, which comprises supplying as the liquid a solution consisting essentially of 5 grams of fish gelatin in a solvent consisting of 8 millilitres of water, 10 millilitres of ethanol and 1 millilitre of peppermint  
25 flavouring.

7. A method according to any one of the preceding claims, which comprising providing an air flow to

encourage the deposition of the at least one fibre or fibrils on the surface.

8. A method according to any one of the preceding  
5 claims, which further comprises regulating the temperature, for example by applying heat, of the region where the liquid issues from the outlet to facilitate the formation of the at least one fibre or fibrils.

10 9. A method according to any one of the preceding claims, which comprises establishing the electric field by applying a high voltage to the surface.

10. A method of manufacturing tablets, comprising:  
15 supplying a liquid consisting essentially of a hydrophilic solution of gelatin to an outlet;  
establishing an electric field between the outlet and a support surface to cause liquid issuing from the outlet to form on the surface a web or mat consisting of  
20 at least one gelatin fibre or gelatin fibrils;  
separating the web or mat into a plurality of individual tablets; and  
incorporating at least one active ingredient and a sweetener such as saccharine into and/or on the tablets.

25

11. A method according to any one of the preceding claims, which comprises using as the surface a rotatable endless surface such as a belt.

12. A method according to any one of the preceding claims, which comprises incorporating the at least one active ingredient by spraying the active ingredient onto at least one of: the at least one fibre or fibrils;  
5 the mat or web; and the individual tablets.

13. A method according to any one of the preceding claims, which comprises incorporating the active ingredient into the at least one fibre or fibrils.  
10

14. A method according to any one of the preceding claims, which comprises forming the at least one fibre of fibrils with a core containing an active ingredient.

15 15. A method of manufacturing a pharmaceutical product which comprises using a method in accordance with any one of the preceding claims and providing as the at least one active ingredient an ingredient which is pharmacologically or biologically active.

20 16. A method of manufacturing a confectionary product which comprises using a method in accordance with any one of claims 1 to 14 to form a plurality of individual tablets and incorporating as the at least one active  
25 ingredient at least one of the following: sugar; chocolate; a flavouring; and a colorant.

17. Apparatus for manufacturing consumable or dissolvable tablets, comprising:

means for supplying a liquid containing a biodissolvable carrier to an outlet;

means for establishing an electric field between the outlet and a support to cause liquid issuing from the outlet to form at least one fibre or fibrils of the biodissolvable carrier which deposit(s) onto the support to form a fibre web or mat;

means for separating the web or mat into a plurality of individual tablets; and

means for incorporating at least one active ingredient in the tablet.

18. Apparatus according to claim 15, wherein the separating means comprises at least one cutter.

15

19. Apparatus for manufacturing consumable or dissolvable tablets, comprising:

means for supplying a liquid containing a biodissolvable carrier to an outlet;

means for establishing an electric field between the outlet and a support to cause liquid issuing from the outlet to form at least one fibre or fibrils of the biodissolvable carrier;

means for causing the fibre or fibrils to deposit onto the support to form a plurality of individual tablets each comprising a fibre web or mat; and

means for incorporating at least one active ingredient into the web or mat.



20. Apparatus according to claim 17, 18 or 19, further comprising, for providing the liquid, a supply of a gelatin, polyvinyl pyridine, polyvinyl alcohol, polysucrose, starch, cellulose, a cellulose derivative, a sugar, a confectionary product such as toffee or caramel.

21. Apparatus according to any one of claims 17 to 19, further comprising, as the liquid, a supply of a solution consisting essentially of 5 grams of gelatin in 7 to 9 millilitres of water and 10 to 11 millilitres of ethanol.

22. Apparatus according to any one of claims 17 to 19, further comprising, as the liquid, a supply of a solution consisting essentially of 5 grams of gelatin in 8 millilitres of water, 10 millilitres of ethanol and 1 millilitre of peppermint flavouring.

23. Apparatus according to any one of claims 17 to 22, further comprising air flow causing means for facilitating the deposition of the at least one fibre or fibrils onto the support.

24. Apparatus according to any one of claims 17 to 23, wherein the electric field establishing means comprises means for applying a positive potential to the support.

25. Apparatus according to any one of claims 17 to 24, further comprising a rotatable endless surface as the support.

26. Apparatus according to any one of claims 17 to 25, further comprising an environmental control means for regulating the temperature of the region where liquid issues from the outlet.

5

27. Apparatus according to any one of claims 17 to 26, further comprising spraying means for spraying the at least one active ingredient onto at least one of: the fibre or fibrils; the mat or web; and individual tablets.

10

28. Apparatus according to any one of claims 17 to 27, further comprising means for supplying the active ingredient so that the at least one fibre or fibrils have a core containing the active ingredient.

15

29. A consumable or dissolvable tablet, pad or mat manufactured using a method in accordance with any one of claims 1 to 16 or apparatus in accordance with any one of claims 17 to 28.

20

30. A consumable or dissolvable tablet comprising a web of fibres of a biodissolvable carrier material carrying at least one active ingredient, the carrier material being arranged to dissolve or disintegrate in a wet environment such as on the tongue or in the mouth of a human being or other animal.

25

31. A consumable or dissolvable tablet comprising a web of fibres or fibrils of gelatin carrying at least one

active ingredient, the tablet being arranged to dissolve or disintegrate in a wet environment such as on the tongue or in the mouth of a human being or other animal.

- 5    32. A tablet according to claims 29, 30 or 31, wherein the active ingredient comprises a pharmacologically or biologically active ingredient.

- 10    33. Use of electrohydrodynamic comminution to produce a consumable or dissolvable tablet.

**FIG. 1**

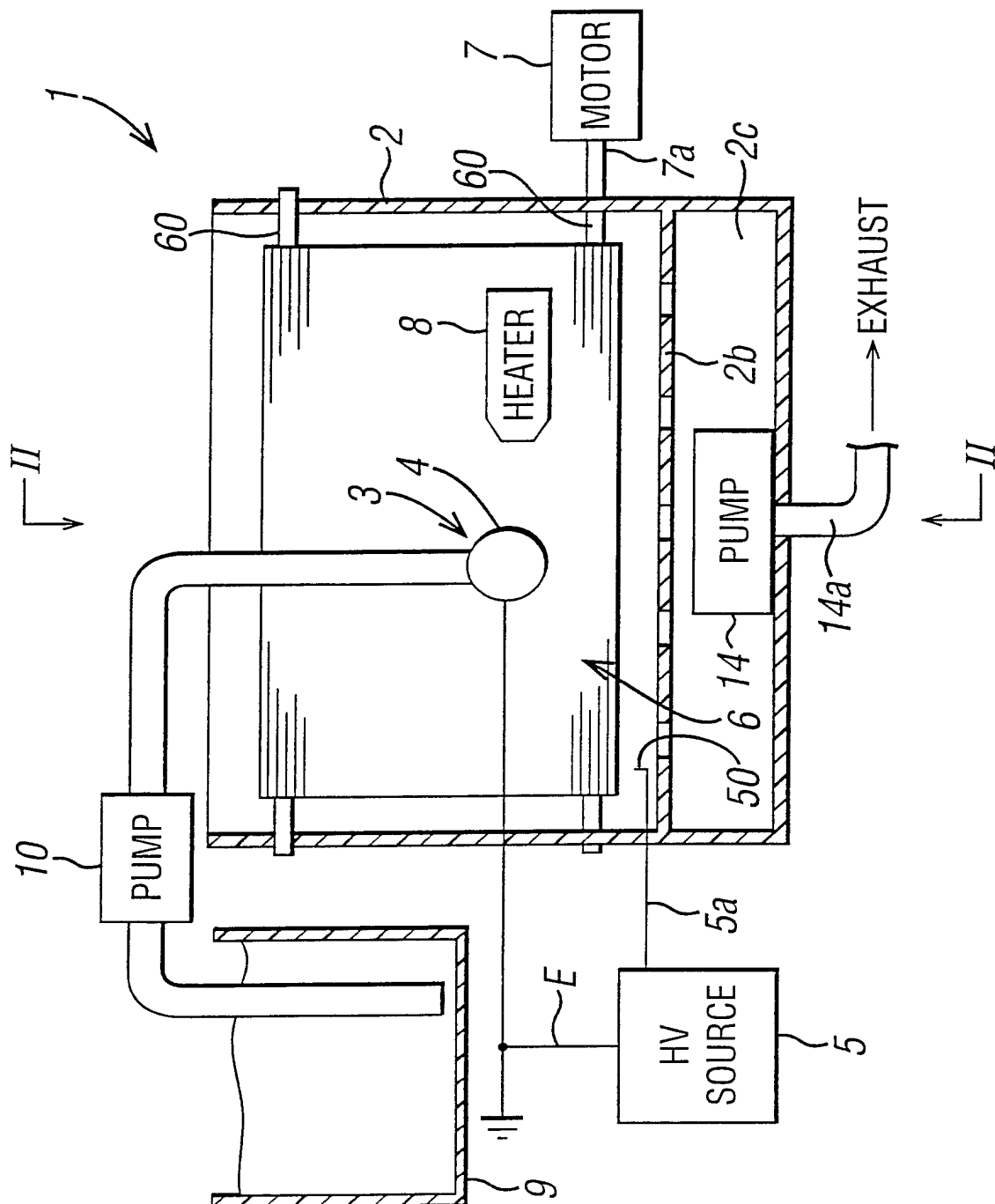


FIG. 2

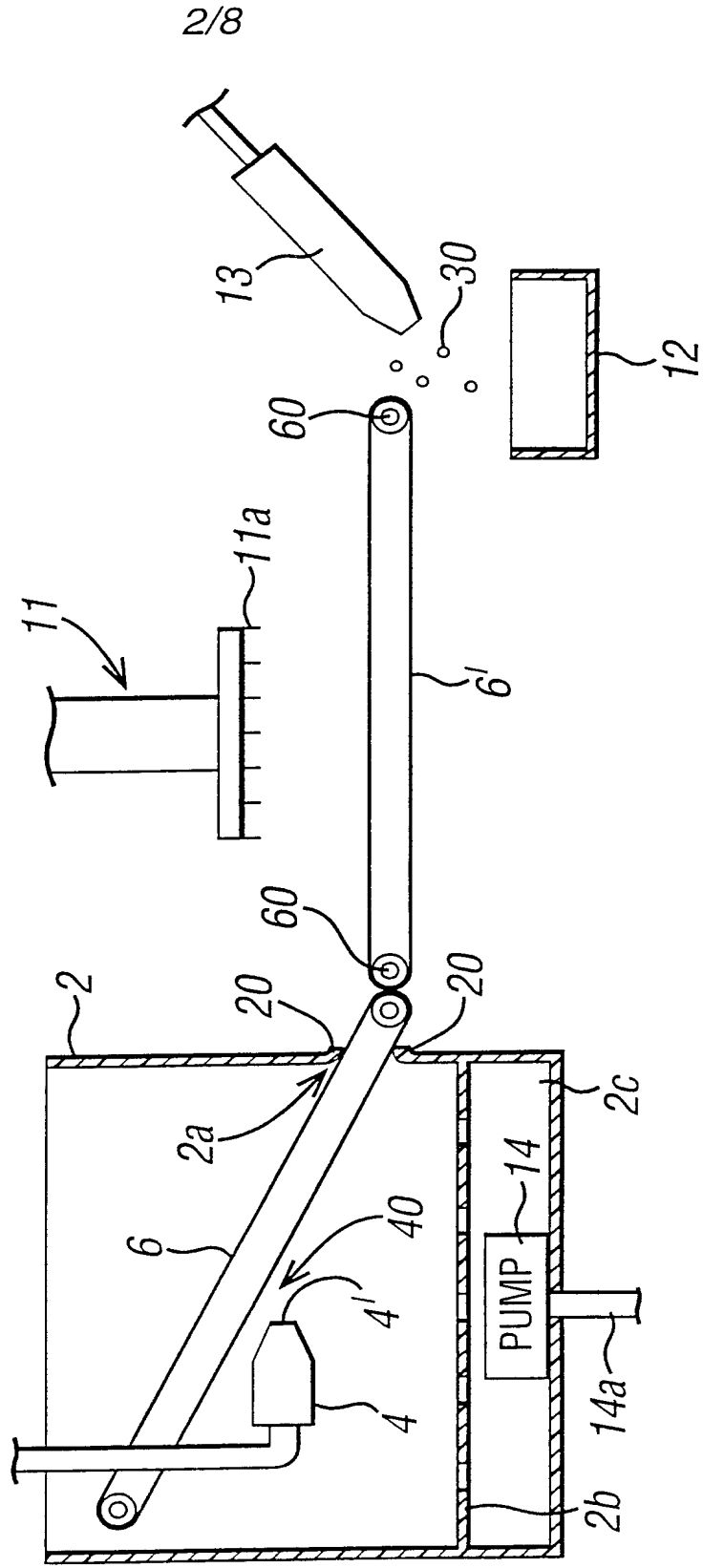
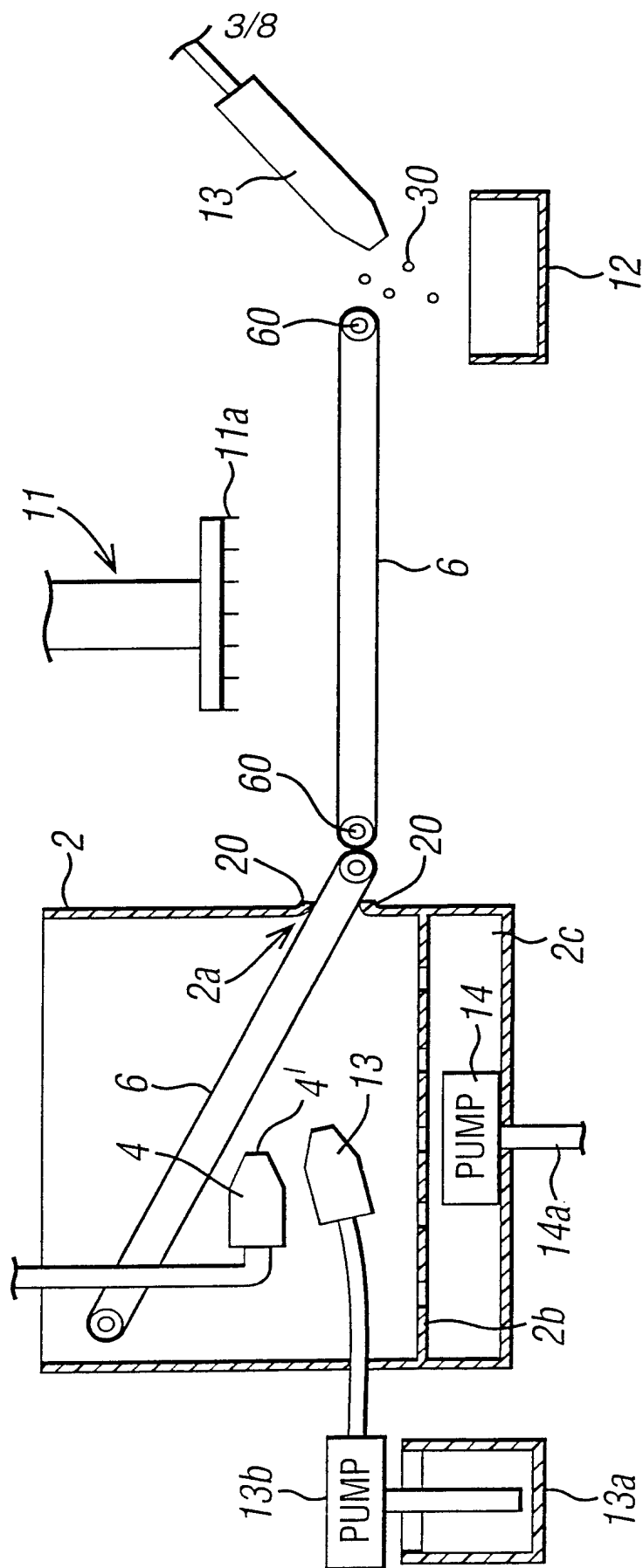


FIG. 3



4/8

FIG. 4

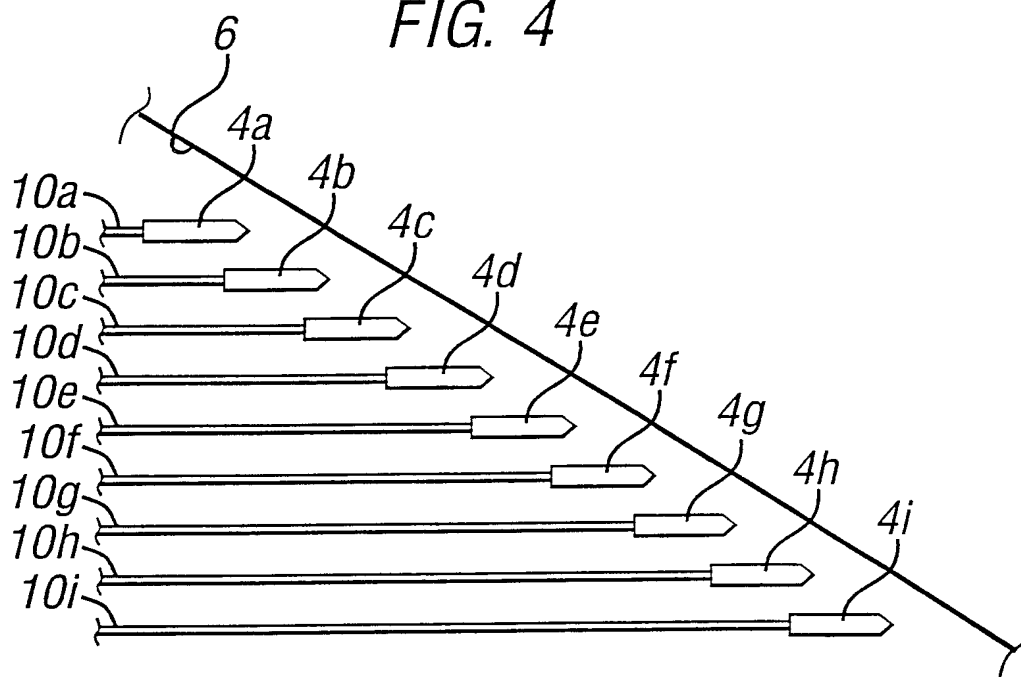


FIG. 6

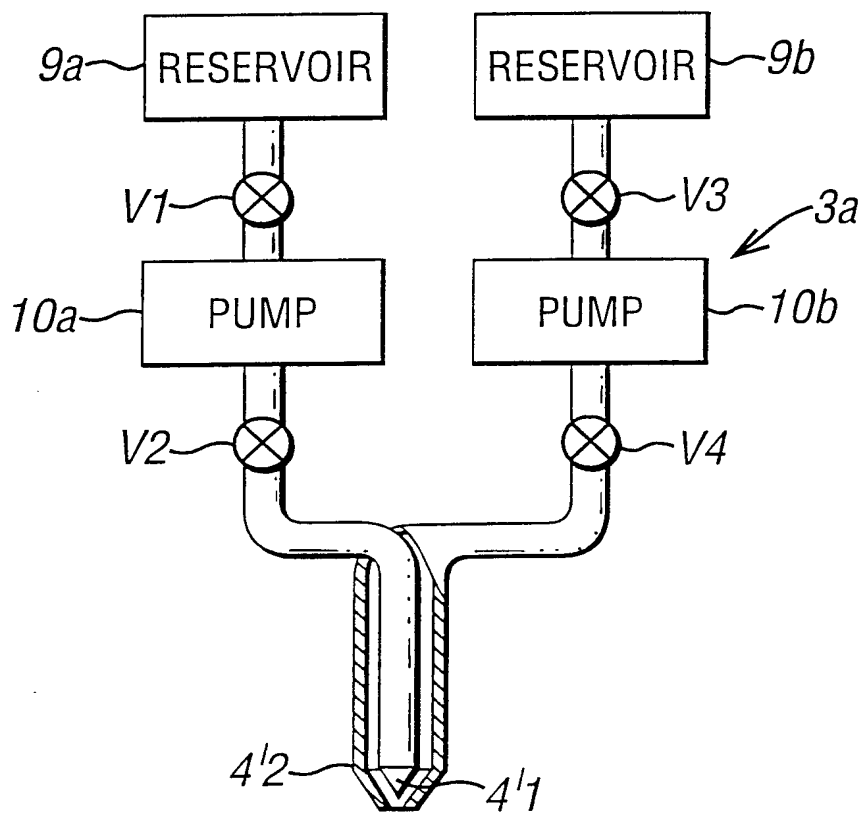
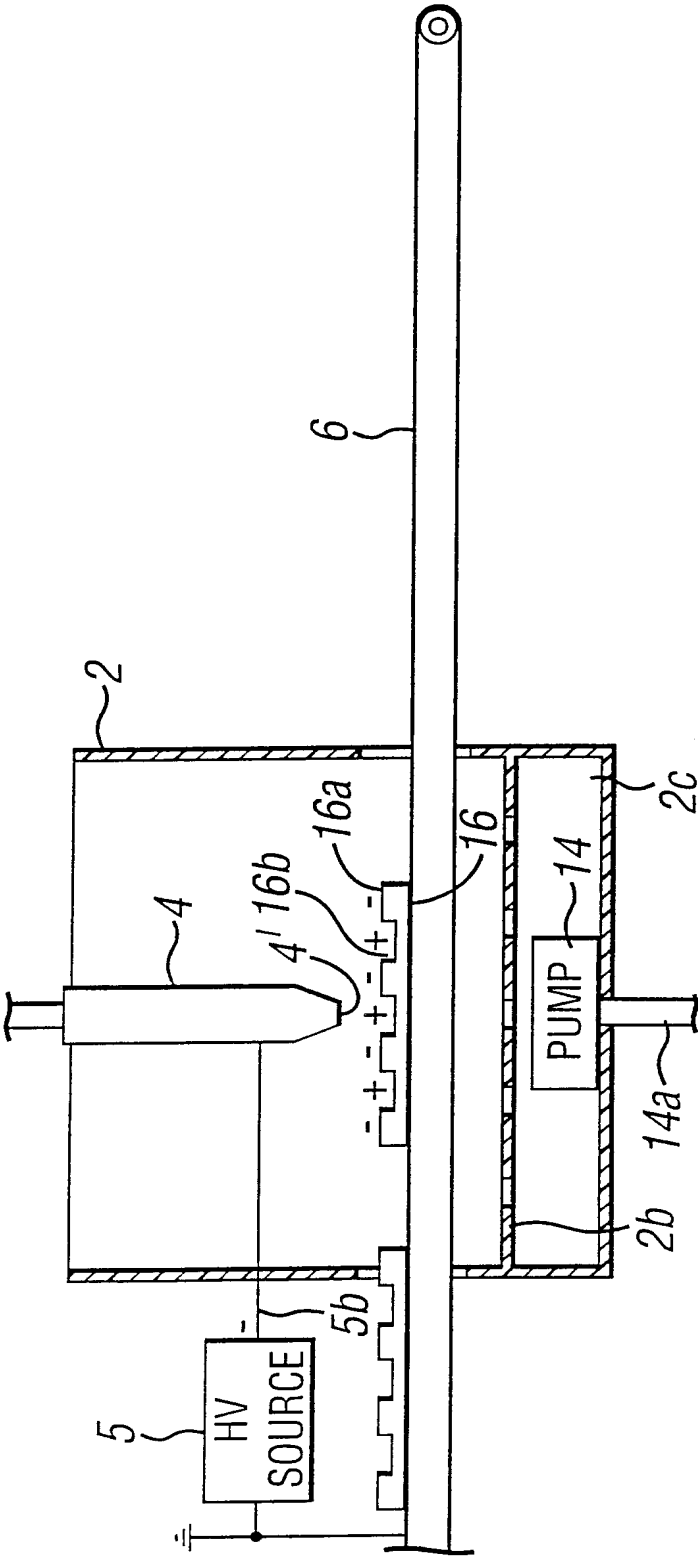


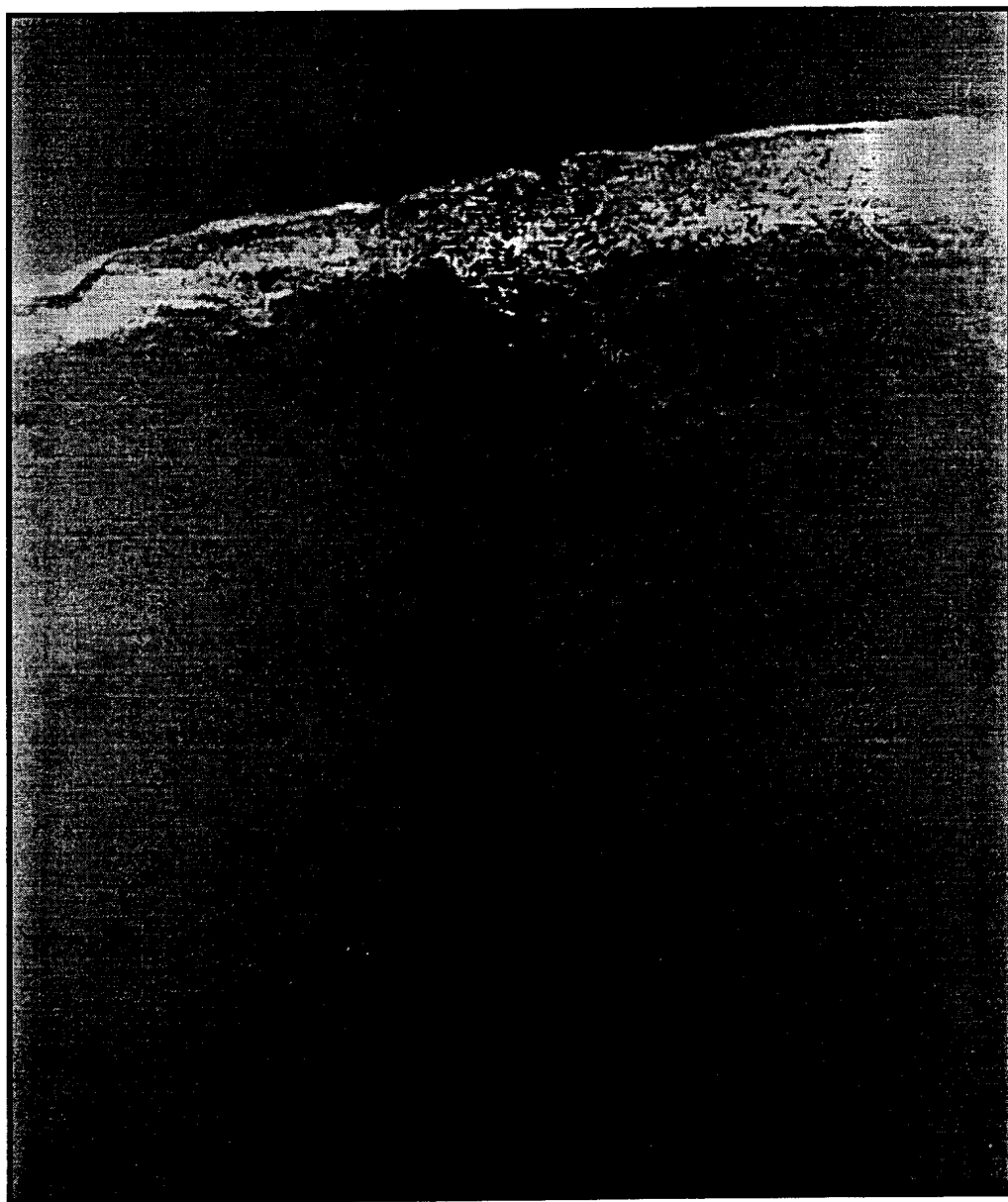
FIG. 5





6/8

*FIG. 7*



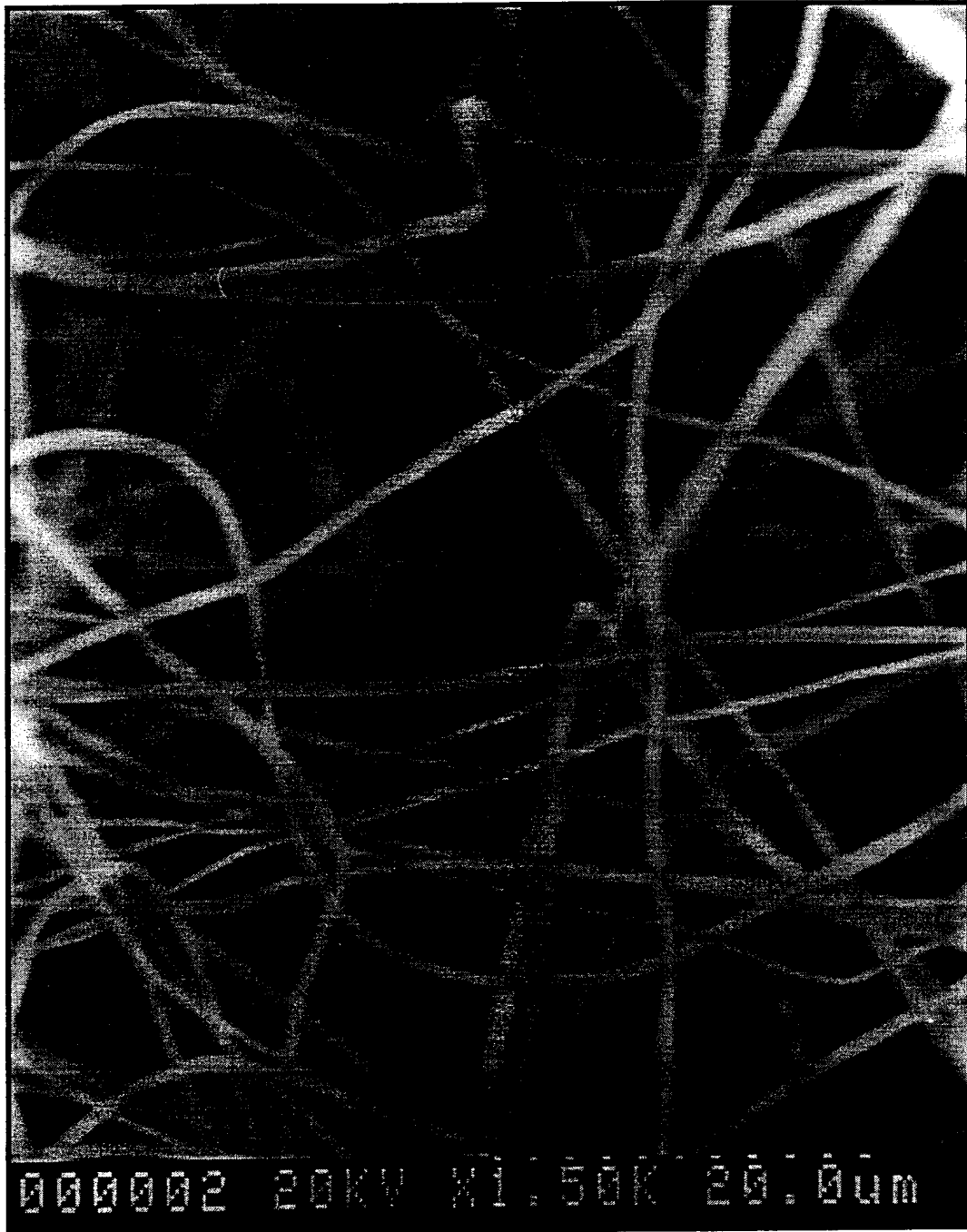
7/8

*FIG. 8*



8/8

*FIG. 9*



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01728

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61J3/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 03267 A (ELECTROSOLS LTD ;COFFEE RONALD ALAN (GB)) 29 January 1998 (1998-01-29) cited in the application claims 1,31,32,37; figures ----	1-7, 9-25, 27-29,33
Y	FR 2 335 206 A (HOFFMANN LA ROCHE) 15 July 1977 (1977-07-15) -----	1-7, 9-25, 27-29,33
X	the whole document -----	30-32
X	US 5 229 164 A (PINS HEINRICH ET AL) 20 July 1993 (1993-07-20) the whole document -----	30-32
X	WO 90 06969 A (FUISZ PHARMACEUTICAL LTD) 28 June 1990 (1990-06-28) claims 47,48 -----	30-32
	----- -/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 August 2000

Date of mailing of the international search report

18/08/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Godot, T

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 00/01728

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 019 929 A (DUDZIK JOACHIM ;DUDZIK WINFRIED (DE))  10 December 1980 (1980-12-10)  abstract</p> <p>-----</p>	30-32

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 00/01728

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9803267 A	29-01-1998	AU 3628497 A EP 0912251 A	10-02-1998 06-05-1999
FR 2335206 A	15-07-1977	US 4029758 A US 4029757 A US 4031200 A AT 365449 B AT 923976 A CA 1085295 A CH 624846 A DE 2656387 A DK 562276 A,B, FI 763597 A,B, GB 1561100 A GR 81307 A IL 51096 A JP 1395182 C JP 52076419 A JP 62000125 B LU 76378 A MC 1117 A NL 7613922 A,B, NO 764242 A,B, NZ 182871 A PH 14489 A PT 65960 A,B SE 438597 B SE 7614123 A US 4072551 A US 4126502 A ZA 7607136 A PH 13712 A US 4126503 A AU 2051976 A ES 454207 A PH 13423 A US 4083741 A PH 16921 A PH 12959 A US 4307555 A US 4349531 A PH 13426 A US 4165998 A PH 17318 A US 4069084 A PH 12825 A US 4069086 A AU 514195 B BE 849377 A CA 1087974 A PH 13279 A PH 16400 A US 4128445 A	14-06-1977 14-06-1977 21-06-1977 11-01-1982 15-06-1981 09-09-1980 31-08-1981 30-06-1977 16-06-1977 16-06-1977 13-02-1980 11-12-1984 16-09-1980 11-08-1987 27-06-1977 06-01-1987 18-01-1978 12-08-1977 17-06-1977 16-06-1977 25-10-1979 07-08-1981 01-01-1977 29-04-1985 25-08-1977 07-02-1978 21-11-1978 26-10-1977 09-09-1980 21-11-1978 22-06-1978 16-03-1978 23-04-1980 11-04-1978 12-04-1984 19-10-1979 29-12-1981 14-09-1982 23-04-1980 28-08-1979 20-07-1984 17-01-1978 31-08-1979 17-01-1978 29-01-1981 14-06-1977 21-10-1980 27-02-1980 22-09-1983 05-12-1978
US 5229164 A	20-07-1993	DE 3545090 C AT 62406 T AU 577213 B AU 6841687 A	25-06-1987 15-04-1991 15-09-1988 15-07-1987

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 00/01728

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
US 5229164	A	CA 1289074 A DE 3678719 D DK 396787 A, B, WO 8703805 A EP 0227050 A EP 0250578 A GR 3002266 T JP 7078018 B JP 63502430 T NO 175038 B	17-09-1991 16-05-1991 29-07-1987 02-07-1987 01-07-1987 07-01-1988 30-12-1992 23-08-1995 14-09-1988 16-05-1994	
WO 9006969	A	28-06-1990	US 5011532 A AT 136735 T AU 645248 B AU 4814690 A BR 8907819 A CA 2005200 A DE 68926307 D EP 0448626 A EP 0687498 A HU 58774 A HU 217035 B IL 92462 A JP 4502492 T KR 157626 B US 5370881 A US 5034421 A US 5028632 A US 5096492 A ZA 8909318 A	30-04-1991 15-05-1996 13-01-1994 10-07-1990 12-11-1991 13-06-1990 23-05-1996 02-10-1991 20-12-1995 30-03-1992 29-11-1999 30-05-1994 07-05-1992 01-12-1998 06-12-1994 23-07-1991 02-07-1991 17-03-1992 26-09-1990
EP 0019929	A	10-12-1980	DE 2922522 A DE 3042916 A JP 55163175 A	04-12-1980 01-07-1982 18-12-1980